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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/038,271 | 10/23/2001 | Frits Jacobus Fallaux | 3833.6US | 8381 |

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| EXAMINER | |
|---|---|
| PRIEBE, SCOTT DAVID | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/038,271 | FALLAUX ET AL. | |
| | Examiner | Art Unit | |
| | Scott D. Priebe, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 Aug. & 14 Sep. 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,30-33,35-38 and 40-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,30-33,35-38 and 40-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050603, 20050812*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Primary Examiner Scott D. Priebe, Ph.D., Group Art Unit 1633.

### *Information Disclosure Statement*

The information disclosure statement filed 6/3/05 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein as Basler et al., Gene 170: 249-254, 1996, has not been considered since no copy of this document was provided.

The information disclosure statement filed 6/3/05 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein as EP 259212 has not been considered since the document is wholly in French.

The Brody et al. document listed on the PTO-1449 of 6/3/05 has been considered. However, it has been crossed off of the PTO-1449, and will therefore not be printed on the face

of a patent, because the citation is incomplete. The citation lacks the volume number of the journal, and a publication date.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 30-33, 35-38, and 40-50 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. It is not clear whether the claims recite an adenoviral DNA to be packaged. The "recombinant nucleic acid" in claims 1 and 40 could be the packaged adenoviral DNA. However, the specification also discloses complementing nucleic acid that meets the limitations of the recombinant nucleic acid as well. Furthermore, it is unclear whether the recombinant nucleic acid is a recombinant adenoviral nucleic acid. Claims 1 and 40 recite the presence of an encapsidation signal and ITR, but fail to specify whether these elements are adenoviral. The claims permit the encapsidation signal to be any encapsidation signal, such as of phage M13 or of a retrovirus. Likewise, the claims permit the ITR to be any ITR, for example an AAV ITR. Consequently, other missing elements from the recombinant nucleic acid are adenoviral sequences encoding all gene products required in *trans* for replication of the recombinant nucleic acid as an adenoviral vector genome other than E1 gene products and either

a second ITR or a free hairpin at the other end, and a recitation that an adenoviral ITR is at one end of the second nucleic acid. An adenoviral genome cannot be replicated if it does not have an ITR at each end. The claim requires the recombinant nucleic acid to include all sequences for its replication, but unless the recombinant nucleic acid is a recombinant adenoviral genome, these sequences could be whatever is required for replication of some other type of nucleic acid, e.g. an AAV vector or plasmid.

This rejection would be overcome by amending claims 1 and 40 to limit the encapsidation signal and ITR to be an adenoviral encapsidation signal and adenoviral ITR, and to specify that the recombinant nucleic acid comprises all sequences required in *trans* for replication of an adenovirus that are not provided by the cell. It is noted however, that amending claim 1 as suggested here would result in claims 1, 3, and 4 being identical in scope to claims 1, 3, and 4, respectively, of US 6,692,966, which would result in statutory double patenting under 35 USC 101.

Claims 1-6, 30-33, 35-38, and 40-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The "recombinant nucleic acid" of the claims is broader than the corresponding subject matter disclosed in the original application. As originally described, the "recombinant nucleic acid" is or comprises a replication defective adenoviral vector genome comprising adenoviral

ITRs, an adenoviral encapsidation signal, and all adenoviral coding sequences required for replication of the vector genome that are not provided by the cell. As indicated in the preceding rejection, the "recombinant nucleic acid" of the claims does not meet these limitations.

Claims 1-6, 30-33, 35-38, and 40-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for producing recombinant adenovirus comprising a gene of interest. The claims are indefinite, being incomplete for lacking sufficient structural elements (indicated above) to achieve the purpose set forth in the preambles of the claims. The claims must explicitly or implicitly indicate that all sequences required, whether in *cis* or *trans*, for replication and packaging of an adenoviral genome are provided by the nucleic acids in the cell. For the same reason, the claims as written are not enabled by the specification.

The specification teaches two basic types of adenovirus which can be made by the claimed processes. The first type are adenovirus having adenoviral genomes which lack early region gene functions in: E1A; E1A and E1B; E2A; E1A and E2A; and E1A, E1B and E2A, and comprise a gene of interest and the remainder of adenoviral genes (E2B, E4, L1-L5, etc.) and all cis elements (ITRs, encapsidation sequence) necessary for replication of adenoviral DNA and production of virions. These adenovirus can be made and/or propagated in cells which comprise nucleic acids encoding and expressing E1A; E1A and E1B; E2A; E1A and E2A; or E1A, E1B and E2A, depending on which of E1A, E1B and E2A are deficient in the adenoviral genome.

The specification does not teach any adenoviral DNA construct capable of generating adenovirus of the first type that does not initially have an ITR at both ends, nor does it even imply such.

The second type of adenovirus are minimal or gutless vectors which lack all adenoviral coding sequence, and comprise two ITRs, an encapsidation sequence, and the gene of interest. With respect to the minimal adenoviral vectors, the specification teaches that the starting adenoviral vector nucleic acid may have either an ITR at each end with a packaging sequence at one end, or an ITR and packaging sequence at one end and at the other end a sequence which can form a hairpin for initiation of second strand synthesis. After second strand synthesis, the latter construct is converted to an inverted repeat of all the starting DNA, such that each end has an ITR and encapsidation sequence. The specification discloses using the hairpin construction to produce helper adenoviral genomes that cannot be packaged because of their large size (inverted duplication of most of the adenoviral genome, i.e. from about nucleotide 3500 to the 3' ITR) and lack of an encapsidation sequence. In order to make and/or propagate this second type of adenovirus, the cell must contain nucleic acid which encodes and expresses all adenoviral gene products required for DNA replication and production of adenoviral particles, e.g. E1A, E1B, E2A, E2B, E4, L1-L5, etc. The specification discloses two example of this where the adenoviral sequences encoding the products needed are provided by an E1 region inserted into the chromosome and the remaining adenoviral *trans* function is provided from either an E1 deleted-helper adenovirus or from a DNA comprising two inverted copies of an adenoviral genome from about nucleotide 3500 to the 3' ITR.

As they are written, the claims are far broader in scope than the enabling disclosure in the specification. Except for claim 2, none of the claims requires a nucleic acid (to be packaged)

having all of the adenoviral sequences required in *cis* for replication and packaging of a recombinant adenoviral genome. Claims 5-17 do not require any of the sequences required in *cis*. None of the claims require all of the adenoviral sequences required in *trans* for replication and propagation of a recombinant adenoviral genome. While not all of the sequences required in *trans* need be present in the recombinant adenoviral genome, they must be present in the cell in order for a recombinant adenovirus to be produced. See specification, paras. 0009-0012, 0021, 0025, 0058, 0064, and 0077 for example, which describe adenoviral sequences required in *cis* and *trans*.

With respect to claims requiring cells having an E2A region for complementing an E2A-deficient adenoviral genome, the specification (paras. 0025-0027) teaches that the E2A gene product must be expressed at high level and is extremely toxic to the cells, and that the only ways to provide the E2A product in trans are: 1) where the E2A product is E2Ats125 and the nucleic acid encoding it is operably linked to a constitutive or inducible promoter or the E2A is wild-type, in which case it must be operably linked to an inducible promoter; or 2) the E2A product is expressed from a helper virus which also provides all the adenoviral products required in *trans* other than the E1 products (which are provided by DNA integrated in the cellular genome).

The claims as written do not require all of the structural and functional adenoviral sequences known in the art to be required for replication of recombinant adenoviral vectors. The omission of elements critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The guidance is quite limited when compared to the breadth of the claims, and the

only working examples disclosed required all of the sequences discussed above for operativity. The specification must teach one of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir., 1991). The claims clearly are not enabled for their full breadth and should be amended to reflect the disclosure.

This part of the rejection would be overcome by the same changes suggested above, but with the same caveat regarding statutory double patenting as well.

With respect to claims 36 and 48, the application contains the PER.C6 cell line, ECACC accession number 96022940, encompassed by the definitions for biological material set forth in 37 C.F.R. § 1.801. Because it is apparent that this cell line is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809. Applicants' assertion that the cell line has been deposited under the Budapest Treaty is noted. However, all of the requirements of C.F.R. §§ 1.801 through 1.809 have not been met. In particular, applicants failed to comply with 37 C.F.R. § 1.808(a)(2). Since the deposit has been made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strains have been deposited under the Budapest Treaty and that the strains will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

***Double Patenting***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (f) he did not himself invent the subject matter sought to be patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 30-33, 35-38, and 40-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 43 and 44 of U.S. Patent No. 6,340,595 or claims 4, 7, 11, 24, 26-28, and 32 of U.S. Patent No. 6,413,776. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the subject matter of the '595 and '776 claims. These patents are assigned to Galapagos Genomics, and cannot be terminally disclaimed.

Claims 1-6, 30-33, 35-38, and 40-50 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The '595 and '776 patents shares only inventor Bout with the instant application.

Claims 1-6, 30-33, 35-38, and 40-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-6 of U.S. Patent No. 6,395,519. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 4-6 of '519 embrace the instantly claimed subject matter, and when read in light of claim 3 of '519 and the supporting disclosure in the '519 patent, which is identical to the instant disclosure, were clearly intended to embrace the variations claimed in the instant application. Claim 4 of '519 does not specify that the cell does not provide pIX. However, claim 3 of '519 is directed to a PER.C6-derived cell that would be used in the method, and this cell lacks pIX coding sequence. The '519 claims also do not require the replication defective adenovirus vector to comprise a gene of interest. However, the '519 specification clearly discloses such an embodiment. The '519 claims also do not specify that the E2A complementing sequence encode the ts125 E2A gene product, but this is disclosed as the preferred embodiment of the '519 invention (Abstract). Instant claims 40-50 are directed simply to an embodiment of claims 1-6, 30-33, 35-38 that was routine in the art for making a cell containing a replication defective adenoviral vector genome, which was also described for making the cell required in claim 4 of '519.

Claims 1-6, 30-33, 35-38, and 40-50 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. Inventor Schouten of the '519 patent is not an inventor on the instant application.

Claims 1-6, 30-33, 35-38, and 40-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No.

6,670,188. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '188 claims embrace the instantly claimed subject matter, and when read in light of supporting disclosure in the '188 patent, which includes the instant disclosure, were clearly intended to embrace the variations claimed in the instant application. The '188 claims are generic with respect to the adenoviral sequences present in the packaging cell; however, the instant claims are directed to embodiments of the '188 claims disclosed in the '188 specification.

Claims 1-6, 30-33, 35-38, and 40-50 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The '188 patent shares only inventor Bout with the instant application.

Claims 1-6, 30-33, 35, 36, and 40-48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-22 and 34 of copending Application No. 10/002,750. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-6, 30-33, 35-38 embrace the subject matter of the '750 claims. Instant claims 40-50 are directed simply to an embodiment of claims 1-6, 30-33, 35-38 that was routine in the art for making a cell containing a replication defective adenoviral vector genome in a packaging cell, which was also described in the '750 application for making the cell required in the '750 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. However, this application has been allowed, and upon issue this rejection will no longer be provisional.

Claims 1-6, 30-33, 35, 36, and 40-48 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The '750 application shares no common inventor with the instant application.

Claims 1-6, 30-33, 35-38, and 40-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 60, 65-69, 95 and 96 of copending Application No. 10/036,949. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the subject matter of the '949 claims wherein the cell used is PER.C6 (claims 67 and 95).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. However, this application has been allowed, and upon issue this rejection will no longer be provisional. It is noted that assignment papers do not appear to have been filed in the '949 application, but its parent application has been assigned to Galapagos Genomics. If the '949 application is not commonly assigned with the instant application, it cannot be terminally disclaimed.

Claims 1-6, 30-33, 35-38, and 40-50 are also rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The '949 application shares only inventor Bout with the instant application.

Claims 1-6, 30-33, 35-38, and 40-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 70-100 of copending Application No. 10/136,139 or claims 1-31 of copending application 11/134,674.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace the subject matter of the '139 claims and '674 claims, which are identical to one another. It is noted that these '139 claims have been withdrawn from consideration as being directed to a non-elected invention. However, as long as these '139 claims are pending, this provisional rejection will be maintained. Cancellation of the non-elected claims in the '139 application would overcome this rejection.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. It is noted that the '674 application does not appear to have been assigned yet. If the '674 application is not assigned to Crucell, it cannot be terminally disclaimed.

The terminal disclaimer filed on 2/2/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Pat. No. 5,994,128 has been reviewed and is accepted.

The terminal disclaimer filed on 5/7/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Pat. No. 6,306,652 has been reviewed and is accepted.

The terminal disclaimers filed on 5/7/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration dates of U.S. Pat. Nos. 6,265,212; 6,306,652; and 6,692,966 have been reviewed and accepted.

The terminal disclaimers filed on 8/12/05 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration dates of any patent(s)

issuing from U.S. Appl. Nos. 10/125,751; 10/219,414; and 10/618,526 have been reviewed and accepted.

The terminal disclaimer filed on 9/14/05 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Pat. Nos. 6,033,908 and 6,306,652 has been reviewed and is accepted.

The terminal disclaimers have been recorded.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633